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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Michael R. Rosen et al.
Serial No.: 09/505, 458.
Filed : February 11, 2000
For : CARDIAC REMODELING

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April 15, 2003

Assistant Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

In compliance with his duty of disclosure under 37 C.F.R. §1.56, applicant directs the Examiner's attention to the following references, which are listed on the accompanying form PTO-1449 (Exhibit 1). Copies of references 1-38 attached hereto as Exhibits 2-38 respectively, except for reference number 17.

1. Page, E. Cardiac Gap Junctions. In: The Heart and Cardiovascular System. H.A. Fozzard, E. Haber, R.B. Jennings, A.M. Katz, and H.E. Morgan (eds). New York: Raven Press Ltd. 1992; 1003-1048. (Exhibit 2)
2. Spach MS, Miller WT III, Dolber PC, Kootsey JM, Sommer JR, Mosher CE Jr. The functional role of structural complexities in the propagation of depolarization in the atrium of the dog. Cardiac conduction disturbances due to

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discontinuities of effective axial resistivity. *Circ Res.* 1982; 50:175-191. (Exhibit 3)

3. Smith JH, Green CR, Peters NS, Rothery S, Severs NJ. Altered patterns of gap junction distribution in ischemic heart disease. An immunohistochemical study of human myocardium using laser scanning confocal microscopy. *Am J Pathol.* 1991; 139:801-821. (Exhibit 4)
4. Luke RA, Saffitz JE. Remodeling of ventricular conduction pathways in healed canine infarct border zones. *J Clin Invest.* 1991; 87:1594-1602. (Exhibit 5)
5. Peters NS, Green CR, Poole-Wilson PA, Severs NJ. Reduced content of connexin43 gap junctions in ventricular myocardium from hypertrophied and ischaemic human hearts. *Circulation.* 1993; 88:864-875. (Exhibit 6)
6. Campos De Carvalho AC, Tanowitz HB, Wittner M, Dermietzel R, Roy C, Hertzberg EL, Spray DC. Gap junction distribution is altered between cardiac myocytes infected with Trypanosoma cruzi. *Circ Res.* 1992; 70:733-742. (Exhibit 7)
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9. Guerrero-P-A; Schuessler-R-B; Davis-L-M; Beyer-E-C; Johnson-C-M; Yamada-K-A; Saffits-J-E: Slow ventricular conduction in mice heterozygous for a connexin43 null mutation. *Journal of Clinical Investigation* 1997;99(8): 1991-1998 (Exhibit 10)
10. Peters NS, Severs NJ, Coromilas J, Wit AL. Disturbed connexin43 gap junctional distribution correlates with the location of reentrant circuits in the epicardial border zone of healing canine infarcts that cause ventricular tachycardia. *Circulation*. 1997 95;988-996 (Exhibit 11)
11. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA: Atrial fibrillation begets atrial fibrillation. *Circulation* 1995;92: 1954-1968. (Exhibit 12)
12. Kajstura-J; Zhang-X; Liu-Y; Szoke-E; Cheng-W; Olivetti-G; Hintze-T-H; Anversa-P: The cellular basis of pacing-induced dilated cardiomyopathy: Myocyte cell loss and myocyte cellular reactive hypertrophy. *Circulation* 1995; 92(8): 2306-2317 (Exhibit 13)
13. Rosenbaum MB, Blanco HH, Elizari MV, Lazzari JO, Davidenko JM: Electronic modulation of the T wave and cardia memory. *Am J Cartel* 1982;50:2130222. (Exhibit 14)
14. Chatterjee K, Harris A, Davies G, Leatham A: Electrocardiographic changes subsequent to artificial ventricular depolarization. *Br Heart J* 1969;31:770-779

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15. Shvilkin A, Danilo P, Jr. Wang J, Burkhoff D, Anyukhovsky EP, Sosunov EA, Hara M. Rosen MR. The evolution and resolution of long-term cardiac memory. Circulation 1998;97:1810-1817. (Exhibit 16)
16. del Balzo U, Rosen MR: T wave changes persisting after ventricular pacing in canine heart are altered by 4-aminopyridine but not by lidocaine. Circulation 1992;85: 1464-1472. (Exhibit 17)
17. Katz AM: T wave "Memory": Possible causal relationship to stress-induced changes in cardiac ion channels? J Cardiovasc Electrophysiol 1992;3:150-159.
18. Tan, RC; Joyner, RW: Electronic influences on action potentials from isolated ventricular cells. Circ Res: 1990;67: 1071-1081) (Exhibit 18)
19. Yu H, McKinnon D, Dixon JE, Gao J, Wymore R, Cohen IS, Danilo, P Jr., Shvilkin A, Anyukhovsky EP, Sosunov EA, Hara M, Rosen MR: The transient outward current, I_{to1} , is altered in cardiac memory. Circulation, 1999; 99:1898-1905. (Exhibit 19)
20. Anyukhovsky EP, Sosunov EA, Feinmark SJ, et al: Effects of quinidine on repolarization in canine epicardium, midmyocardium, and endocardium: II. In vivo study. Circulation 1997;96:4019-4026. (Exhibit 20)
21. Anyukhovsky EP, Sosunov EA, Gainullin RZ, Rosen MR. The

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22. Yeh-H-I; Dupont-E; Coppen-S; Rothery-S; Severs-N-J: Gap junction localization and connexin expression in cytochemically identified endothelial cells of arterial tissue. Journal of Histochemistry and Cytochemistry 1997; 45(4): 539-550 (Exhibit 22)
23. Hoyt RH, Cohen ML, Saffitz JE. Distribution and three-dimensional structure of intercellular junctions in canine myocardium. Circ. Res. 1989;64:563-574. (Exhibit 23)
24. Peters NS, Wit AL. Myocardial architecture and ventricular arrhythmogenesis. Circulation 1998;97: 1746-1754. (Exhibit 24)
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26. Wit AL, Janse MJ: Basic mechanisms of arrhythmias, in *The Ventricular Arrhythmias of Ischemia and Infarction*. New York, Futura, 1992, pp. 1-160. (Exhibit 26)
27. Lesh MD, Pring M, Spear JF: Cellular uncoupling can unmask dispersion of action potential duration in ventricular myocardium. Circ. Res. 1989;65:1426-1440. (Exhibit 27)
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29. Yue-L; Feng-J; Gaspo-R; Li-G-R; Wang-Z; Nattel-S: Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. Circulation Research 1997;81(4): 512-525. (Exhibit 29)
30. Quan W, Rudy Y: unidirectional block and reentry of cardiac excitation: a model study. Circ. Res. 1990;66:367-382. (Exhibit 30)
31. Van-Der-Velden-Huub-M-W; Van-Kempen-Marjan-J-A; Wijffels-Maurits-C-E-F; Van-Zijverden-Maaike; Groenewegen-W-Antoinette; Allessie-Maurits-A; Jongsma-Habo-J: Altered pattern of connexin40 distribution in persistent atrial fibrillation in the goat. Journal-of-Cardiovascular-Electrophysiology. June, 1998;9(6)595-607. (Exhibit 31)
32. Patel P, Jones DG, Hadjinicolou L, Glenville B, Stanbridge R, Severs NJ, Peters NS. Changes in human atrial connexin expression in atrial fibrillation and ischemic heart disease. Circulation 1997;96(8):I-17. (Exhibit 32)
33. U.S. Patent No. 3,937,226 to Funke (Exhibit 33)
34. U.S. Patent No. 4,088,140 to Rockland et al. (Exhibit 34)
35. U.S. Patent No. 4,628,937 to Hess et al. (Exhibit 35)
36. U.S. Patent No. 4,787,389 to Tarjan (Exhibit 36)
37. U.S. Patent No. 5,174,289 to Cohen (Exhibit 37); and
38. U.S. Patent No. 5,243,978 to Duffin (Exhibit 38)

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If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

Because this Information Disclosure Statement is being filed with a Request For Continued Examination, no fee is believed to be due.

Respectfully submitted,



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